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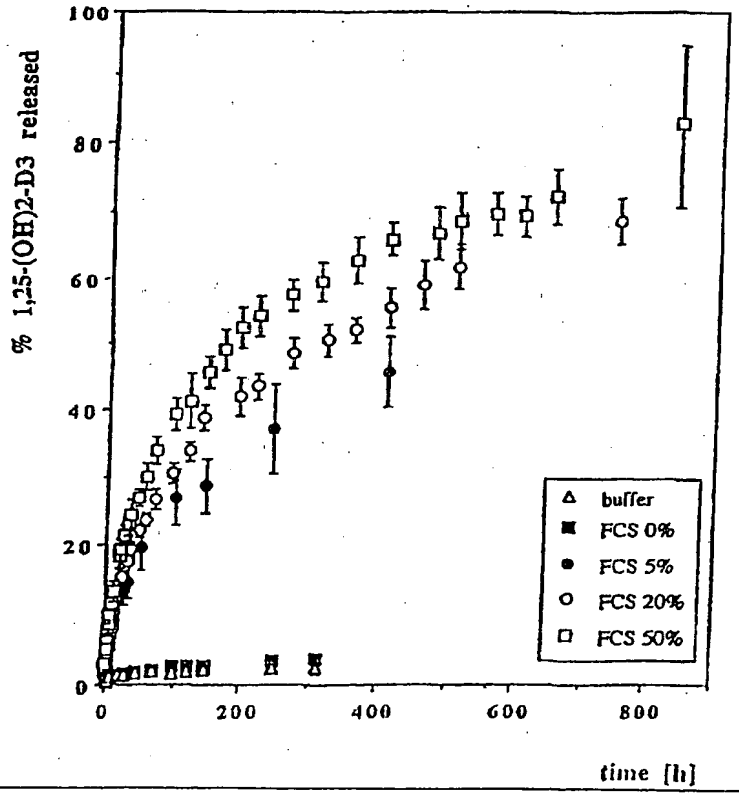
(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING VITAMIN-D ANALOGS

(57) Abstract

A controlled-release pharmaceutical preparation comprises a Vitamin-D analog in a supporting matrix, alone or together with pharmaceutically acceptable additives or active agents.



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PHARMACEUTICAL COMPOSITIONS COMPRISING VITAMIN-D ANALOGS

Field of The Invention

The present invention relates to the field of pharmacy. More particularly, the invention relates to novel slow-release pharmaceutical preparations containing Vitamin-D analogs.

BACKGROUND OF THE INVENTION

The Vitamin-D hormone, 1,25-dihydroxyvitamin D_3, is known to be active anti-proliferation agents which is active against a variety of cancer cells, including cells of the large intestine [A. Belelli et al., *Carcinogenesis*, **13**, 2293-2298, 1992]. The activity of 1,25-dihydroxyvitamin D_3 was tested in rats colon cancer and it was found that once weekly administration for 5 weeks reduced by 50% the number of DMH-induced murine colon cancer. However, the potentially useful therapeutic activity of 1,25-dihydroxyvitamin D_3 has so far been hampered by its high calcemic activity. Treatment of rats with higher doses of 1,25-dihydroxyvitamin D_3, by subcutaneous injection, which could potentially be beneficial in cancer treatment, led to hypercalcemia and death.

The Prior Art

A variety of vitamin-D hormone analogs have been developed [G. Jones and M. Calverly, *TEM Vol.. 4*, No. 9, 297-303, 1993], mainly searching for

noncalcemic, but still anticancer-effective analogs, but with no success. Most analogs known so far have either maintained their high calcemic activity, or have lost their effectiveness or stability.

Therefore, the great therapeutic potential of 1,25-dihydroxyvitamin D_3 and its analogs has remained so-far unexploited.

Summary of the Invention

It is an object of the present invention to provide pharmaceutical preparations comprising 1,25-dihydroxyvitamin D_3 or other vitamin D analogs thereof, which can be used to treat patients without leading to substantial hypercalcemia effects.

It is another object of the invention to provide slow-release pharmaceutical preparations comprising 1,25-dihydroxyvitamin D_3 or other vitamin D analogs thereof, as an active ingredient.

It is a further object of the invention to provide pharmaceutical preparations which can be used to supply highly bioavailable amounts of 1,25-dihydroxyvitamin D_3 or analogs thereof, in a controlled manner.

It is still another object of the invention to provide a method for treating a patient suffering from an illness which responds to vitamin D-analogs treatment, particularly cancer patients, psoriasis patients or patients with unbalanced mineral homeostasis, by administration of slow-release active compositions.

The primary objects of the invention are achieved by providing controlled-release pharmaceutical preparations comprising a Vitamin-D analog in a supporting matrix, typically a polymeric matrix.

Other objects of the invention will become apparent as the description proceeds.

Brief Description of the Drawings

In the drawings:

Fig. 1 shows the kinetics of 1,25-dihydroxyvitamin D_3 release from an EVA-based matrix, dependent on fetal calf serum concentrations;

Fig. 2 shows the effect of 1,25-dihydroxyvitamin D_3 loading in the matrix of Fig. 1, on its released fraction;

Fig. 3 shows the effect of implantation site *in-vivo* on the serum concentration of 1,25-dihydroxyvitamin D_3, following two weeks post-implantation, with a load of 0.0050% of 1,25-dihydroxyvitamin D_3;

Fig. 4 shows the effect of implantation site *in-vivo* on the serum concentration of Ca^{+2}, after two weeks post-implantation, with the same matrix as in Fig. 3;

Fig. 5 shows the effect of 1,25-dihydroxyvitamin D_3 released on the activity of ornithine decarboxylase (ODC) in DMH-treated rats (Example 3); and

Fig. 6 shows the effect of 1,25-dihydroxyvitamin D_3 released according to the invention, and injected (prior art), on the activity of ornithine decarboxylase (ODC) in DMH-treated rats.

Detailed Description of The Invention

As stated above, in one aspect the invention is directed to controlled-release pharmaceutical preparations comprising a Vitamin-D analog in a supporting matrix, alone or together with pharmaceutically acceptable additives or active agents. Vitamin analogs are many, and will be recognized by the skilled person. Illustrative and non-limitative examples of such analogs include 1,25-$(OH)_2D_3$ (calcitrol), 26,27-F_6-1,25-$(OH)_2D_3$ (ST-630), 1α-$(OH)D_2$, 1α-$(OH)D_3$, 1,24-$(OH)_2D_3$ (TV-02), 22-oxacalcitriol (OCT), calcipotriol (MC 903), 1,25-$(OH)_2$-16-ene-23-yne-D_3 (Ro 23-7553), EB 1089 and ED-71. The term "analog", in the context of the present invention, is meant to include synthetic analogs as well as Vitamin-D metabolites.

According to a preferred embodiment of the invention the matrix is a polymeric matrix. Polymeric materials and matrices useful in drug delivery systems are well known in the art, and need not be discussed in detail. For a detailed discussion of such systems reference is made to Robert Langer, *SCIENCE, Vol. 249,* pp. 1527-1533, 28 September, 1990,

and to Richard L. Dunn, "Polymeric Matrices", in *POLYMERIC DRUG AND DRUG DELIVERY SYSTEMS*, R. L. Dunn and R. M. Ottenbrite Eds., American Chemical Society, Washington, D.C., 1991. As will be apparent to the skilled person, the polymeric matrix may be of a variety of types. For instance, water-soluble polymers may be employed, such as polyethylene glycol, poly(vinyl alcohol), poly(vinyl pyrrolidone), poly(2-hydroxymethyl methacrylate), poly(acrylamide), hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, gelatin, starch, dextran, sodium alginate, poly(acrylic acid), poly(methacrylic acid), poly(maleic acid half esters), poly(sodium styrene sulfonate), poly(dimethylaminoethyl methacrylate), poly(vinyl pyridine), cellulose acetate N,N-diethylaminoacetate; other suitable polymers include biodegradable polymers, such as poly(meleic anhydride copolymers), gelatine-formaldehyde, acrylamide-N,N'-methylenebisacrylamide, fumaric acid/polyethylene glycol-N-vinyl-pyrrolidone, polylactic acid, polyglycolic acid, polycaprolactone, polyhydroxybutyrate, polyhydroxyvalerate, polyanhydrides, polyorthoesters, poly(amino acids), and polyphosphazenes; or nonbiodegradable polymers, such as silicones, poly(ethylene vinyl acetate), poly(methyl methacrylate), polyethylene, polyurethanes, polyisobutylene, cellulose acetate, poly(ethyl methacrylate) and poly(butyl methacrylate). Other suitable polymers will be recognized by the skilled person.

It has been found that one particularly convenient polymeric matrix is a matrix based on a poly-ethylene-vinyl-acetate copolymer. This matrix will be used in the examples to follow, it being understood that this is only an

illustrative matrix and the invention is in no way limited to this or any other matrix.

The inventors have found that, in order to obtain an optimal release effect of the vitamin-D analog, it is important that release from the polymeric matrix be effected through the formation of a complex between the vitamin-D analog and the vitamin-D binding protein (DBP) which is found in body fluids. Only the complex is substantially soluble in aqueous media, and thus only the complex is immediately and gradually bioavailable. Thus, according to a preferred embodiment of the invention the pharmaceutical preparation is such that the release of the Vitamin-D analog is permitted or promoted by the presence of the Vitamin-D binding protein (DBP).

While, as stated, the DBP is normally provided by body fluids, the invention also encompasses preparations wherein the DBP is provided in the polymeric matrix, to overcome a DBP deficiency at the site of administration, or to promote vitamin-D - DBP complex release.

A preferred Vitamin-D analog to be used in conjunction with the invention is 1,25-dihydroxyvitamin D_3. However, the invention is in no way meant to be limited to this specific compound, and any other suitable and pharmaceutically valuable analog thereof can be used.

The invention is also directed to a pharmaceutical composition for the treatment of cancer, comprising an effective amount of a preparation according to the invention. While the invention is useful in the treatment

of a variety of cancers, one particularly difficultly treated cancer, which can be treated according to the invention, is colon cancer.

Thus the invention provides a method of treating a cancer patient, comprising administering to the patient in need thereof an anti-cancer effective amount of a preparation as described herein. The slow-release pharmaceutical preparations of the invention may be administered orally, transdermally or by implantation. Suitable slow-release compositions of the type described above will be recognized by the skilled person. According to a preferred embodiment of the invention the pharmaceutical composition is implanted. Preferably, but non limitatively, the implantation is effected intraperitoneal.

The invention further provides a method of treating patients suffering from imbalanced mineral homeostasis, who need constant correction of their serum vitamin D levels. An example is the group of uremic patients, but of course the invention is not limited to this group.

All the above and other characteristics and advantages of the invention will be better understood through the following illustrative and non-limitative examples.

Preparation A

Matrix Preparation

Drug delivery matrices, based on poly(ethylene-vinyl-acetate) copolymer (EVA) were prepared by solvent casting as described by Rhine et al. [*J. of Pharmaceutical Sciences,* 69, 265-270, 1980]. 1,25-dihydroxyvitamin D_3 - ethanol solution was added to the EVA-methylene chloride solution and casted on dry ice. Loading was calculated as dry weight of 1,25-dihydroxyvitamin D_3 to dry weight of the matrix. Part of the 1,25-dihydroxyvitamin D_3 (1:70,000) was radiolabeled as 1,25-dihydroxy[26,27-methyl-^{3}H]cholecalciferol. This was used in the *in vitro* experiments. Radiolabeled 1,25-dihydroxyvitamin D_3 was not included in matrices used in *in vivo* experiments.

Example 1

In Vitro Release

The release of the radiolabeled 1,25-dihydroxy[26,27-methyl-^{3}H]cholecalciferol was detected by β-counter as a function of time. The matrices were immersed in fetal calf serum (FCS) medium, containing the Vitamin-D binding protein (DBP).

1,25-Dihydroxyvitamin D_3 release was studied in a Backman LS 1800 Series Liquid Scintillation System. The results are shown in Figs. 1 and 2. Fig. 1 shows the effect of serum concentration in the medium. It can easily be seen that virtually no 1,25-dihydroxyvitamin D_3 release occurs in the

absence of DBP (buffer and FCS 0%), and that the release rate increases with increasing FCS (and hence DBP) concentrations.

Fig. 2 shows the percentage of released 1,25-dihydroxyvitamin D_3 as a function of its load in the matrix (at 50% FCS). At high loads a lower percentage is released, in contrast to known diffusion dependent EVA systems, and suggesting that the release of $1,25(OH)_2D_3$ depends on the ratio between DBP and $1,25(OH)_2D_3$.

Example 2

Effect of Implantation Site

Tumor induction experiments with rats were carried out according to the procedures described in the aforementioned Belleli et al. article, and their description is incorporated herein by reference, for the sake of brevity. 12 rats were used in the experiment, according to the following groups:

1) 8 rats as a control group, were given the EVA matrix without any 1,25-dihydroxyvitamin D_3;

2) 4 rats were given implants of about 0.1 gr of 0.0050% 1,25-dihydroxyvitamin D_3 in an EVA matrix.

The rats were treated with 1,2-dimethylhydrazine (DMH), after 2 weeks, according to the procedure of Belleli et al., to induce colon cancer.

The matrices were implanted i.p.. Blood samples were withdrawn after two weeks, and the concentration of 1,25-dihydroxyvitamin D_3 and of

Ca^{+2} were measured. In all cases EVA matrices were used, with a load of 0.0050% of 1,25-dihydroxyvitamin D_3.

The results are shown in Fig. 3, for 1,25-dihydroxyvitamin D_3, and in Fig. 4 for Ca^{+2}. The control was as specified above.

From the results it is evident that implantation in the peritoneum is substantially more effective than subcutaneous implantation. Without wishing to be bound by any particular theory, the inventors believe that this difference may derive from the fact that body fluids are abundant in the peritoneum, and therefore DBP is more readily available there, to release 1,25-dihydroxyvitamin D_3 from the polymeric matrix. The 1,25-dihydroxyvitamin D_3 released is biologically active, as expressed by the increase in serum calcium levels (Fig. 4).

Example 3

Early Stage Inhibition

The activity level of ODC in DMH-treated rats were measured, at 48 hours after DMH induction. ODC activity is believed to be associated with the initiation stage of colon carcinogenesis. [D.H. Russell et al., Drug. Metab. Rev., 16, 1-88, 1981. G.D. Luk et al., Cancer Res., 46, 4449-4452, 1986]. If so, the ODC activity peak may serve as a reliable marker for colon carcinogenesis. A radiometric technique which measures the amount of $^{14}CO_2$ stoichiometrically released from labeled ornitine substrate

during the decarboxylation reaction was used. The matrix was implanted i.p. two weeks before DMH induction.

The results are shown in Fig. 5. The values shown in the figure have the following meanings:

"vehicle"	- control rats without DMH induction.
"control"	- matrix without the drug with DMH.
"Vit.D3 low"	- 0.0025% loading of Vitamin-D analog with DMH
"Vit.D3 high"	- 0.0050% loading of Vitamin-D analog with DMH

The results indicate that the ODC activity obtained with a Vit.D3 loading of 0.0050% approaches that of the vehicle. It therefore appears that the preparation of the invention interferes with early stages of colon carcinogenesis.

Example 4

Example 3 was repeated, but additionally two additional rat groups were treated with DMH for another 4 weeks until frank colon cancer. The 1st group served as control and the 2nd group consisted of animals with implanted EVAc matrices (about 0.1g) loaded with 0.0050% 1,25-$(OH)_2D_3$.

16 weeks after the 1st DMH treatment the rats were killed and the number and distribution of the grossly visible tumors were independently

scored by at least two observers. In the control group (5 rats) colonic tumors were present - average, 5 tumors/rat. By contrast, in the 1,25-$(OH)_2D_3$ treated rats (4 rats) no tumors were observed. The results obtained 48 hours after the first DMH injection are shown in Fig. 6. These results are seen to be in agreement with those of Fig. 5.

All the above has been provided for the purpose of illustration, and is not intended to limit the invention in any way. Many modifications are possible, as will be appreciated by the skilled person, in the various active ingredients, matrices and administration methods. For instance, additional beneficial agents can be incorporated in the matrix, which can be released together with the vitamin-D analog, or at different times, various implantation locations are possible, as well as different administration methods, e.g., by ingestion, all without exceeding the scope of the invention.

CLAIMS

1. A controlled-release pharmaceutical preparation comprising a Vitamin-D analog in a supporting matrix, alone or together with pharmaceutically acceptable additives or active agents.

2. A pharmaceutical preparation according to claim 1, wherein the matrix is a polymeric matrix.

3. A pharmaceutical preparation according to claim 2, wherein the polymeric matrix is based on a poly-ethylene-vinyl-acetate copolymer.

4. A pharmaceutical preparation according to any one of claims 1 to 3, wherein the release of the Vitamin-D analog is permitted or promoted by the presence of the Vitamin-D binding protein (DBP).

5. A pharmaceutical preparation according to claim 4, wherein the DBP is provided by body fluids.

6. A pharmaceutical preparation according to claim 4, wherein the DBP is provided in the polymeric matrix.

7. A pharmaceutical preparation according to any one of claims 1 to 6, wherein the Vitamin-D analog is 1,25-dihydroxyvitamin D_3.

8. A pharmaceutical composition for the treatment of cancer, comprising an effective amount of a preparation according to any one of claims 1 to 7.

9. A pharmaceutical composition according to claim 8, wherein the cancer is colon cancer.

10. A method of treating a cancer patient, comprising administering to the patient in need thereof an anti-cancer effective amount of a preparation according to any one of claims 1 to 7.

11. A method according to claim 10, wherein the cancer is colon cancer.

12. A pharmaceutical composition for the treatment of illnesses associated with low serum vitamin D levels, or which respond to vitamin D treatment, comprising an effective amount of a preparation according to any one of claims 1 to 7.

13. A pharmaceutical composition according to claim 12, wherein the illness is imbalanced mineral homeostasis.

14. A pharmaceutical composition according to claim 12, wherein the illness is psoriasis.

15. A method of increasing serum vitamin D or vitamin D-analog levels, comprising administering to the patient in need thereof an effective amount of a preparation according to any one of claims 1 to 7.

16. A method according to claim 15, wherein the pharmaceutical composition is implanted.

17. A method according to claim 16, wherein the implantation is effected intraperitoneal.

18. A pharmaceutical preparation according to any one of claims 1 to 14, which is suitable for oral administration.

19. A pharmaceutical preparation according to any one of claims 1 to 14, which is suitable for transdermal administration.

20. Use of a Vitamin-D analog-containing matrix, for the preparation of a medicament.

21. A controlled-release pharmaceutical preparation, substantially as described.

AMENDED CLAIMS

[received by the International Bureau on 11 December 1995 (11.12.95); original claims 1-21 replaced by amended claims 1-28 (5 pages)]

1. A controlled-release pharmaceutical preparation comprising a Vitamin-D analog in a supporting matrix, alone or together with pharmaceutically acceptable additives or active agents.

2. A pharmaceutical preparation according to claim 1, wherein the matrix is a polymeric matrix.

3. A pharmaceutical preparation according to claim 2 wherein said polymeric matrix is based on polymers or copolymers selected from the group consisting of water-soluble polymers or copolymers, biodegradeable polymers or copolymers, and nonbiodegradeable polymers or copolymers.

4. A pharmaceutical preparation according to claim 3 wherein said polymeric matrix is based on water-soluble polymers or copolymers selected from the group consisting of polyethylene glycol, poly(vinyl alcohol), poly(vinyl pyrrolidone), poly(2-hydroxymethyl methacrylate), poly(acrylamide), hydroxypropyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, gelatin, starch, dextran, sodium alginate, poly(acrylic acid), poly(methacrylic acid), poly(maleic acid half esters), poly(sodium styrene sulfonate), poly(dimethylaminoethyl methacrylate), poly(vinyl pyridine) and cellulose acetate N,N-diethylaminoacetate.

5. A pharmaceutical preparation according to claim 3 wherein said polymeric matrix is based on biodegradeable polymers or copolymers selected from the group consisting of poly(maleic anhydride copolymers), gelatine-formaldehyde, acrylamide-N,N'-methylenebisacrylamide, fumaric acid/polyethylene glycol-N-vinylpyrrolidone, polylactic acid, polyglycolic acid, polycaprolactone,

polyhydroxybutyrate, polyhydroxyvalerate, polyanhydrides, polyorthoesters,poly(amino acids), and polyphosphazenes.

6. A pharmaceutical preparation according to claim 3 wherein said polymeric matrix is based on non-biodegradeable polymers or copolymers selected from the group consisting of silicones, poly(ethylene vinyl acetate), poly(methyl methacrylate), polyethylene, polyurethanes, polyisobutylene, cellulose acetate, poly(ethyl methacrylate) arid poly(butyl methacrylate).

7. A pharmaceutical preparation according to claim 6, wherein the polymeric matrix is based on a poly-ethylene-vinyl-acetate copolymer.

8. A pharmaceutical preparation according to any one of claims 1 to 7, wherein the release of the Vitamin-D analog is permitted or promoted by the presence of the Vitamin-D binding protein (DBP).

9. A pharmaceutical preparation according to claim, 8, wherein the DBP is provided by body fluids.

10. A pharmaceutical preparation according to claim 8, wherein the DBP is provided in the polymeric matrix.

11. A pharmaceutical preparation according to any one of claims 1 to 10, wherein the Vitamin-D analog is selected from the group consisting of: [1,25-dihydroxyvitamin D_3[1,25-$(OH)_2D_3$(calcitrol)], 26,27-F_6- 1,25-$(OH)_2D_3$ (ST-630), 1α-$(OH)D_2$, 1α-$(OH)D_3$, 1,24-$(OH_2)D_3$ (TV-02, 22-oxacalcitriol (OCT),

calcipotriol (MC 903), 1,25-$(OH)_2$-16-ene-23-yne-D_3 (Ro 23-7553), EB 1089 and ED-71.

12. A pharmaceutical preparation according to claim 11, wherein the Vitamin-D analog is 1,25-dihydroxyvitamin D_3.

13. A pharmaceutical preparation according to any one of clams 1 to 12 for use in the manufacture of a pharmaceutical composition for the treatment of illnesses responding to treatment with Vitamin-D analogs.

14. A pharmaceutical preparation for use in the manufacture of a pharmaceutical composition according to claim 13, for the treatment of illnesses selected from the group consisting of cancer, psoriasis and unbalanced mineral homeostasis.

15. A pharmaceutical composition for the treatment of cancer, comprising an effective amount of a preparation according to any one of claims 1 to 12.

16. A pharmaceutical composition according to claim 15, wherein the cancer is colon cancer.

17. A method of treating a cancer patient, comprising administering to the patient in need thereof an anti-cancer effective amount of a preparation according to any one acclaims 1 to 12.

18. A method according to claim 17, wherein the cancer is colon cancer.

19. A pharmaceutical composition for the treatment of illnesses associated with low serum vitamin D levels, or which respond to vitamin D treatment, comprising an effective amount of a preparation according to any one of claims 1 - 12.

20. A pharmaceutical composition according to claim 19, wherein the illness is imbalanced mineral homeostasis.

21. A pharmaceutical composition according to claim 19, wherein the illness is psoriasis.

22. A method of increasing serum vitamin D or vitamin-D analog levels, comprising administering to the patient in need thereof an effective amount of a preparation according to any one of claims 1 - 12.

23. A method according to claim 22, wherein the pharmaceutical composition is implanted.

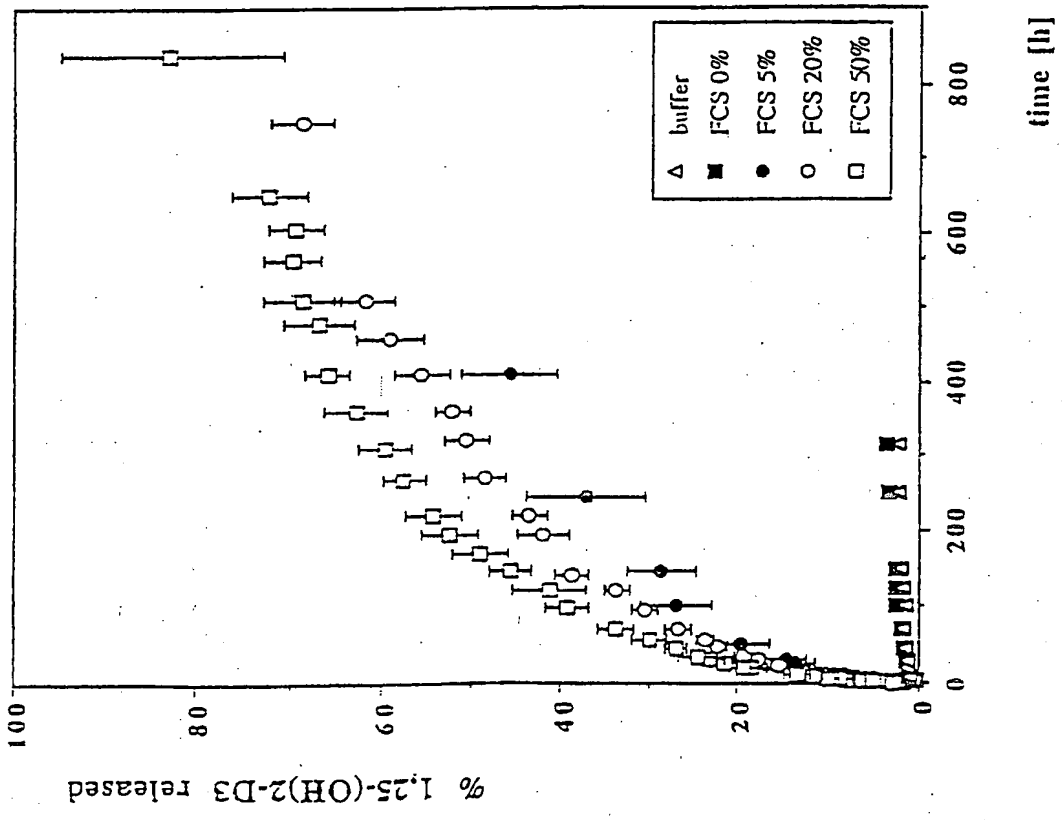
24. A method to claim 23, wherein the implantation is effected intraperitoneally.

25. A pharmaceutical preparation according to any one of claims 1 - 12, which is suitable for oral administration.

26. A pharmaceutical preparation according to any one of claims 1 - 12, which is suitable for transdermal administration.

27. Use of a Vitamin-D analog-containing matrix, for the preparation of a medicament.

28. A controlled-release pharmaceutical preparation, substantially as described.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time [h]
buffer
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FCS 20%
FCS 50%
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20
40
60
80
100
0
200
400
600
800

Fig. 1

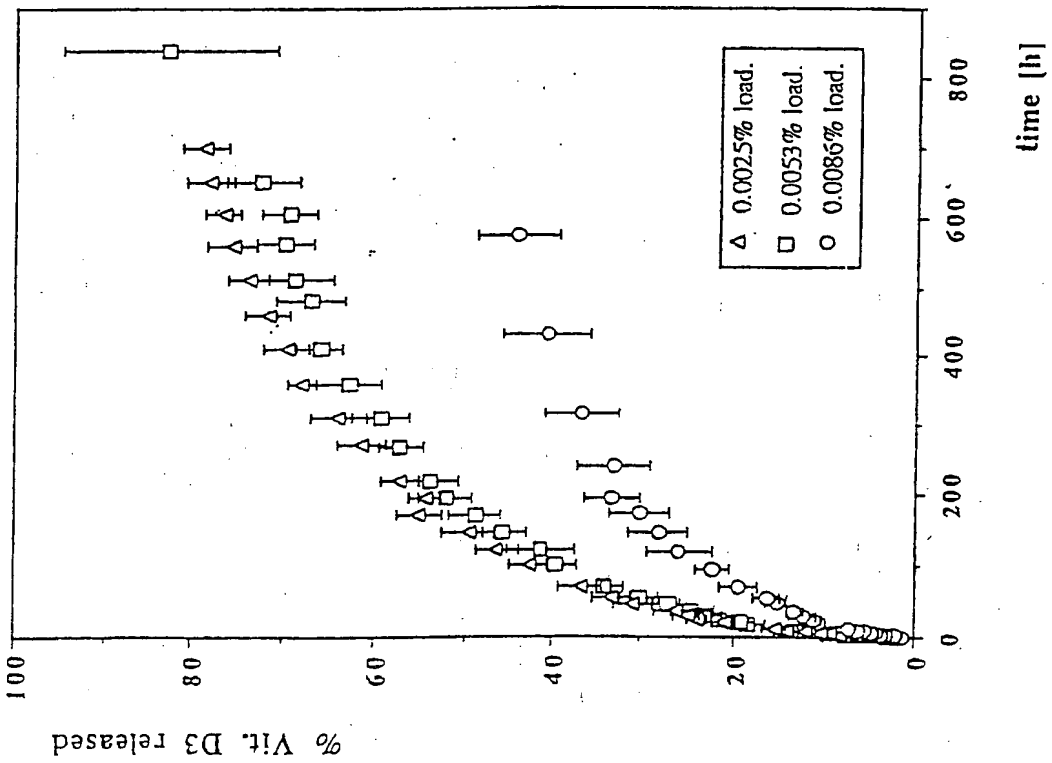
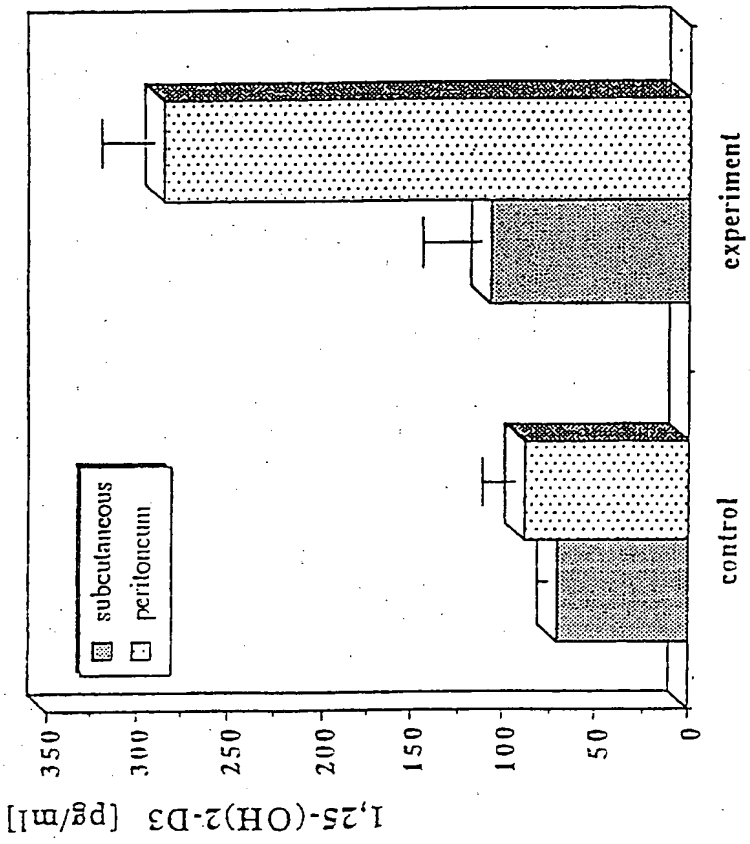

% Vit. D3 released
100
80
60
40
20
0
0
200
400
600
800
time [h]
0.0025% load.
0.0053% load.
0.0086% load.

Fig. 2

Fig. 3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300
250
200
150
100
50
0
subcutaneous
peritoneum
control
experiment

Fig. 4

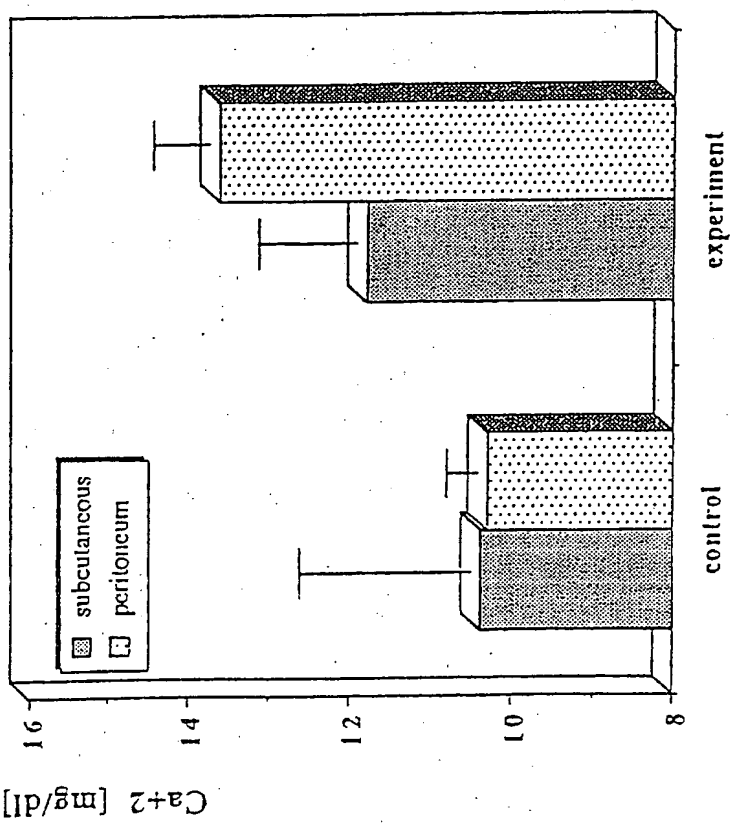

Ca+2 [mg/dl]
16
14
12
10
8
subcutaneous
peritoneum
control
experiment

Fig. 5

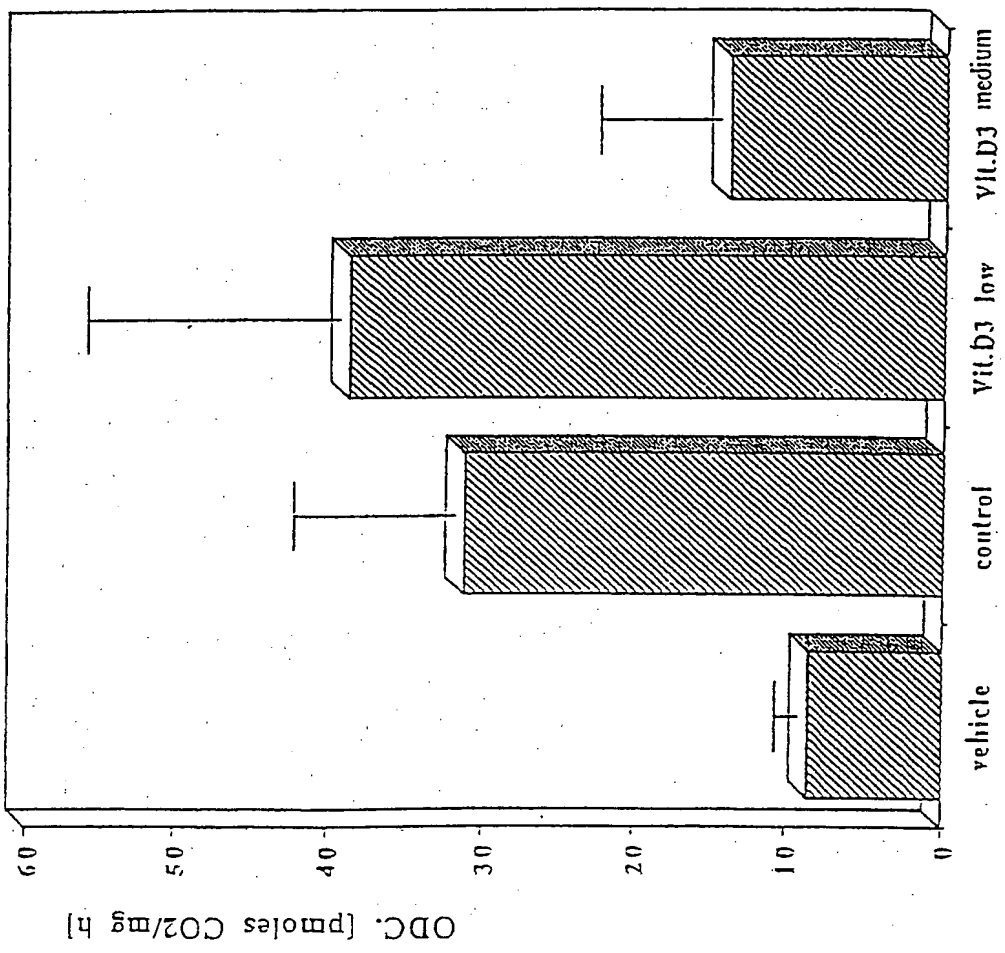
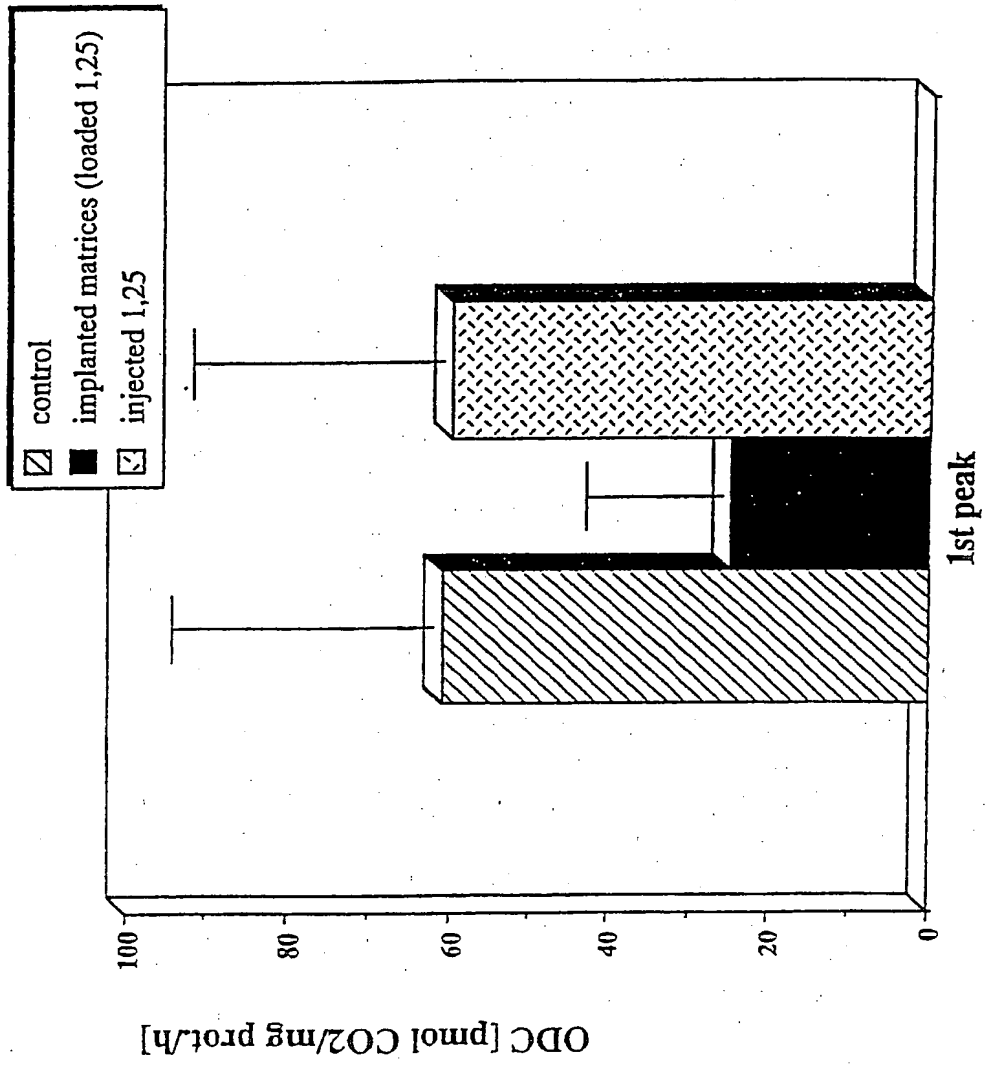

ODC. [pmoles CO2/mg h]
0
10
20
30
40
50
60
vehicle
control
Vit.D3 low
Vit.D3 medium

Fig. 6


control
implanted matrices (loaded 1,25)
injected 1,25
1st peak
ODC [pmol CO2/mg prot./h]
100
80
60
40
20
0

INTERNATIONAL SEARCH REPORT

PCT/US 95/08005

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/59 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,90 09179 (UNIVERSITY OF GEORGIA RESEARCH FOUNDATION,INC.,U.S.A.) 23 August 1990 see claims 1,5,10,13-17,21 see page 12, line 26 - line 31	1,2,7, 12,13, 15,16,21
A	EP,A,0 567 353 (WISCONSIN ALUMNI RESEARCH FOUNDATION,U.S.A.) 27 October 1993 see claims 1,9 see page 4, line 1 - line 8	1,2,7, 12,13, 15,16,21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 1995	13. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	CHEMICAL ABSTRACTS, vol. 122, no. 14, 3 April 1995, Columbus, Ohio, US; abstract no. 169978, see abstract & PROC. INT. SYMP. CONTROLLED RELEASE BIOACT. MATER., 1994 pages 525 - 526 C. SEGAL ET AL. 'POLYMERIC CONTROLLED DELIVERY SYSTEM OF 1,25-DIHYDROXYVITAMIN D3:DEVELOPMENT,CHARACTERIZATION AND APPLICATION IN CHEMOPREVENTION OF COLON CANCER' -----	1-21

INTERNATIONAL SEARCH REPORT

1. .national application No.

PCT/US95/08005

Box I _ Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10-11, 15-17
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 10-11,15-17 are directed to a method of treatment of the human body by therapy (Rule 39.1 (V) PCT), the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9009179	23-08-90	AU-B-	5185790	05-09-90
		US-A-	5366736	22-11-94
		US-A-	5154925	13-10-92
		US-A-	5316770	31-05-94
EP-A-0567353	27-10-93	JP-A-	6009405	18-01-94
		US-A-	5393749	28-02-95